REMARKS

Claims 1, 29 and 30 are amended herein. No new matter is presented.

Claim 1 is amended to recite that a capsule which comprises (1) a granule consisting essentially of a) as an active ingredient, an indoline compound represented by the formula recited in the claim, b) D-mannitol and c) partially pregelatinized starch; and (2) as an extragranular ingredient d) a lubricant selected from magnesium stearate, calcium stearate or talc and e) lauryl sulfate.

Support is found for example in the description of Examples 1 and 2 in the specification, in which the lubricant and sodium lauryl sulfate are added as an extragranular ingredient to the granule.

Upon entry of the Amendment, claims 1, 8, 9, 11, 12, and 27-31 will be all of the claims pending in the application.

I. Response to Claim Rejections - 35 U.S.C. § 112

Claims 1, 8, 9, 11, 12 and 27-31 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite with respect to the recitation of trademark/trade names STARCH 1500 and PCS.

The claims are amended herein to delete the recitation of STARCH 1500" and "PCS", thereby rendering the rejection moot.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

II. Response to Claim Rejection — 35 U.S.C. §103

Claims 1, 8, 9, 11, 12 and 27-31 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Kitazawa et al., (US 5,387,603) in view of Ishihara et al., (US 2002/0177593)

and in further view of Salpekar et al., (US 4,757,090), Shah (US 5,370,878) and Tasaka et al., (US 2002/0173526).

Applicants respectfully traverse the rejection.

The Present Invention

Claim 1 is amended to recite that a capsule which comprises (1) a granule consisting essentially of a) as an active ingredient, an indoline compound represented by the formula recited in the claim, b) D-mannitol and c) partially pregelatinized starch; and (2) as an extragranular ingredient d) a lubricant selected from magnesium stearate, calcium stearate or talc and e) lauryl sulfate.

The capsule of the present invention exhibits an immediate dissolution property in water in which the active ingredient of KMD-3213 is hardly soluble, and has an excellent therapeutic activity for the treatment of dysuria. The capsule of the present invention also has excellent storage stability. Further, the capsule of the present invention has good manufacturing aptitude without causing filling problems during encapsulating process and with a high content uniformity, and is suitable for industrial production.

The disclosure of Kitazawa (US5, 387,603)

Kitazawa merely discloses a compound of KMD-3213 that is useful as a therapeutic agent for treating dysuria at columns 49 to 50 as Compound 40 in the specification. Kitazawa fails to teach or suggest the capsule of the present invention and the advantageous effects of the present capsule.

The disclosure of Ishihara (US2002/0177593)

Ishihara discloses formulation Examples 1 to 6 at pages 51, and 55 to 56 in the specification. The formulations are all tablet containing lactose, corn starch and stearic acid. The

dosage forms and compositions of the formulation Examples 1 to 6 are quite different from those of the capsule of the present invention.

Ishihara also generally mentions Formulations, Administration Routes and Dosages at pages 43 to 46. A number of ingredients used as bulking agents, lubricants, binders, disintegrators are listed in the specification (paragraphs [0589] to [06271). However, Ishihara merely teaches that those ingredients are usually used as a pharmaceutical carrier for preparing solid formulations. Ishihara fails to teach or suggest the capsule of the present invention and the advantageous effects of the present capsule.

The disclosure of Shar (US 5,370,878)

Shar discloses a method for preparing a granulated acetaminophen composition suitable for direct compression into tablets.

The method comprises:

(A) blending a mixture of (a) from about 70 to about 95 percent of acetaminophen by dry weight of the blend, (b) binder, (c) disintegrating agent, (d) lubricant, and (e) a small amount of water or alcohol;

(B) compacting the blend of Step A to form a compact; and

(C) milling the compact Step B to form the granulated acetaminophen composition (column 3, lines 19-27).

Shar describes at column 2, line 68 to column 3, line 4 in the specification that "Acetaminophen is usually marketed in 325ing and 500mg tablets. These tablets have a high dosage level of the drug and are large in size. Accordingly, the tablet blend must contain a high weight of acetaminophen, e.g., about 70 to 95."

Granulated acetaminophen compositions prepared from a mixture of (a) about 90 weight percent of acetaminophen, (b) povidone as a binder, (c) pregelatinized starch (Starch 1500) and croscarmellose sodium as a disintegrating agent, (d) stearic acid and colloidal silicon dioxide as a lubricant, and (e) water are disclosed in Examples 1 to 9.

The granulated acetaminophen compositions of Shar have the characteristics of containing a high dosage level of acetaminophen in tablets, and being suitable for direct compression into tablets without tedious and costly process of wet granulation (column 3, lines 27 to 33). The dosage form and compositions of Shar are quite different from the capsule of the present invention. Thus, Shar fails to teach or suggest the capsule of the present invention and the advantageous effects of the present capsule.

The disclosure of Salpekar (US 4,757,090)

Salpekar discloses a direct tabletting, free-flowing particulate pharmaceutical composition containing N-acetyl-p-aminophenol, which is capable of being directly formed into a tablet having high hardness, short disintegration time and short dissolution time.

The particulate N-acetyl-p-aminophenol composition comprises as components: (a) from about 84 to 94 percent, based on the dry weight of the composition, of N-acetyl-p-aminophenol, (b) pregelatinized starch, and (c) water, said composition being prepared in a fluid bed granulator-dryer by the process which comprises spraying an aqueous slurry of a portion of the pregelatinized starch onto a fluidized composition comprising N-acetyl-p-aminophenol and the remainder of the pregelatinized starch; and drying the resulting granules (claim 1).

Several acetaminophen particulate compositions are disclosed in Examples I to IV in the specification. For example, Example I discloses an acetaminophen particulate composition prepared from 90.0 weight percent of acetaminophen, pregelatinized starch and stearic acid.

Although Salpekar teaches pregelatinized starch, Salpekar fails to teach or suggest partially pregelatinized starch.

The particulate N-acetyl-p-aminophenol compositions of Salpekar, as well as Shar, have the characteristics of containing a high dosage level of acetaminophen in tablets, and being suitable for direct compression into tablets without the need for admixing tabletting adjuvants or aids (column 1, lines 35 to 38). Salpekar fails to teach or suggest the capsule of the present invention and the advantageous effects of the present capsule.

The disclosure of Tasaka (US 2002/0173526)

Tasaka teaches a number of disintegrating agents including partially pregelatinized starch (PCS) on page 15, paragraph [289]. Tasaka also teaches that those disintegrating agents disintegrate a granule by absorbing water in contact with water, causing swelling.

However, in a case where an active ingredient is hardly soluble in water, quickly disintegrating formulations take frequently long dissolution time to be dissolved from the disintegrated formulation. Thus, Tasaka fails to teach or suggest the capsule of the present invention and the advantageous effects of the present capsule.

Distinction over Kitazawa (US 5,387,603) in view of Ishihara (US 2002/0177593) and in further view of Salpekar (US 4,757,090) and Shar (US 5,370,878) and Tasaka (US 2002/017526).

Shar teaches use of partially pregelatinized starch for a short dissolution time. As described above, the granulated acetaminophen composition of Shar is prepared by blending of a mixture of (a) acetaminophen, (b) binder, (c) disintegrating agent, (d) lubricant, and (e) water or alcohol; compacting the blend; and milling the compact.

Comparing the granulated composition of Shar with the capsule of the present invention, the granulated composition of Shar differs from the granule of the present capsule in the point that the granulated composition of Shar does not contain D-mannitol.

Applicants have prepared such comparative capsules, i.e., Capsules N and O, not containing D-mannitol as shown in Table 1 of the attached Supplemental Declaration under 37 C.F.R. § 1.132. The dissolution rates of Capsules N and O are notably lower than those of the Examples 1 and 2 of the present invention (the dissolution rate after 15 minutes: Capsule N: 0.6%; Capsule O: 32%; Example 1: 93%; and Example 2: 97%). In Table 1, Capsule B was prepared, which corresponds to a capsule adding D-mannitol as an intragranular ingredient to Capsule N. The dissolution rate of Capsule B is also notably lower than those of the Examples 1 and 2 of the present invention (the dissolution rate after 15 minutes: Capsule B: 8%; Example 1: 93%; and Example 2: 97%).

A comparison of Capsules N, O and B with Examples 1, 2 and Capsule C shows that not only partially pregelatinized starch but also D-mannitol and sodium lauryl sulfate are necessary for imparting the immediate dissolution property.

As described at column 4, lines 29 to 22, the granulated composition of Shar contains at least a portion of lubricant as an intragranular ingredient while the capsule of the present contains lubricants as an extragranular ingredient. A comparative capsule, i.e., Capsule Q, containing sodium lauryl sulfate as an intragranular ingredient was prepared as shown in Table 1. The dissolution rate of Capsule Q is considerably lower than those of Examples 1 and 2 of the present invention (the dissolution rates: Capsule Q 18% after 5 minutes, 67% after 15 minutes; Example 1: 75% after 5 minutes, 93% after 15 minutes; and Example 2: 77% after 5 minutes, 97% after 15 minutes). Furthermore, a storage stability test was conducted under 60 °C for 7

days with respect to Capsule Q. As a result, Capsule Q showed remarkable decomposition and was unstable while Examples 1 and 2 of the present invention exhibited excellent stabilities (the amount of decomposed product: Capsule Q: 7.44%; Example 1: 0.71%; and Example 2: 0.46%). These results show that sodium lauryl salfate is necessary as an extragranular ingredient for imparting immediate dissolution property and good storage stability.

In view of the above, Applicants submit that the teaching of Shar on partially pregelatinized starch would not lead a person ordinarily skilled in the art to expect the advantageous effects of immediate dissolution and excellent storage stability exhibited by the present invention.

Salpekar teaches that use of pregelatinized starch attributes to a short dissolution time. Salpekar does not teach partially pregelatinized starch.

The particulate N-acetyl-p-aminophenol composition of Salpekar is prepared in a fluid bed granulator-dryer by spraying an aqueous slurry of a portion of the pregelatinized starch onto a fluidized composition comprising N-acetyl-p-aminophenol and the remainder of the pregelatinized starch.

The particulate composition of Salpekar, as well as Shar, is different from the capsule of the present invention in the point that the particulate composition of Salpekar does not contain D-mannitol. As described above, the dissolution rate of capsules not containing D-mannitol in the particulate, are notably lower than those of the capsule of the present invention.

Salpekar also teaches that the particulate composition may further include a, compressibility-promoting binder that provide the hardness of tablets formed from the composition on. column 3, lines 30 to 44, in the specification. Those ordinarily skilled in the art could readily understand that the addition of binders would probably lower the dissolution rate of

tablets formed form the composition since such binders promoting compressibility of tablets usually decrease the disintegration property of the tablets.

As stated above, the capsules of the present invention and the advantageous effects on immediate dissolution and excellent storage stability exhibited by the present invention are not unobvious over Salpekar.

Regarding D-mannitol, the Examiner states in the Non- Final Office Action that Ishihara teaches D-mannitol.

However, the granulated compositions of Shar and Salpekar have the characteristics of containing a high dosage level of acetaminophen in tablets, and being suitable for direct compression into tablets without the need for admixing tabletting adjuvants or aids. In the Declaration under 37 C.F.R. § 1.132 filed April 8, 2010, Applicants have already shown the results that the dissolution rate of the Capsules 1A and 2A containing a high dosage level of KMD-3213 in place of acetaminophen according to the formulations disclosed in Shar and Salpekar, are notably lower as compared with those of the capsules of the present invention or Tablets 1 and 2 of Shar and Salpekar. In the Declaration of April 8, 2010, it was also explained that those notable differences of dissolution rates between KMD-3213 and acetaminophen result from the difference of their physicochemical properties such as water solubility.

Thus, there is no motivation that would lead a person ordinarily skilled in the art to combine the granulated compositions containing highly water soluble acetaminophen for direct compression into tables as taught by Shar or Salpekar with D-mannitol taught by Ishihara for developing capsules containing hardly water soluble KMD-3213 in place of acetaminophen and having immediate dissolution property and good storage stability.

Regarding lubricants, the Examiner states in the Non- Final Office Action that "Salpekar teaches adding compatible mixtures of two or more lubricants such as sodium lauryl sulfate, magnesium stearate. These amounts are such that disintegration, dissolution time will not be increased".

On the contrary, combination use of lubricant and sodium lauryl sulfate as an extragranular ingredient provides the capsule of the present invention with much higher dissolution properties as compared to capsules containing a lubricant alone. Further, the addition of sodium, lauryl sulfate as an extragranular ingredient provides the capsule of the present invention with extremely higher storage stability as compared to capsules containing sodium lauryl sulfate as an intragranular ingredient.

Salpekar fails to teach or suggest the unexpected advantageous effects of decreasing dissolution time and increasing storage stability acbieved by combination use of lubricant and sodium lauryl sulfate as an extragranular ingredient.

The Examiner states in the Non-Final Action that Ishihara teaches that "The pharmaceutical compositions are taught to be produced according to a conventional method in the field, for example, a method described in the Japanese Pharmacopoeia ([0619])". However, the Japanese Pharmacopoeia, XIV edition, the version of which had been published at the time of filling the present U.S. application, merely teaches as follows:

> "Capsules are usually prepared by the following methods.
>
> (i) Hard capsules: Drugs or uniform mixtures of drugs with diluents and other suitable excipients, granules prepared by a suitable method, or granules coated with a suitable coating agent are filled as they are or prepared lightly into hard capsules.
>
> (ii) Soft capsules: Drugs or mixtures of drugs and suitable diluents, etc, are enclosed by an approved suitable capsule base

> such as gelatin plasticized by addition of glycerin, sorbitol, etc., and molded in a suitable shape. If necessary, coloring agents, preservatives, etc. may be added to capsule bases."

The disclosure of the preparation method for capsules in the Japanese Pharmacopoeia fails to teach or suggest the capsule of the present invention and the advantageous effects of the present invention.

Thus, the capsule of the present invention provides unexpectedly superior results over the prior art. Specifically, the capsules of the present invention and the advantageous effects on immediate dissolution property and storage stability of the present invention are not obvious over Kitazawa in view of Ishihara and in further view of Salpekar and Shar and Tasaka. For these additional reasons, the present invention is not rendered obvious by the cited references, whether taken alone or in combination.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

/Jennifer M. Hayes/
Jennifer M. Hayes
Registration No. 40,641

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860
WASHINGTON OFFICE
23373
CUSTOMER NUMBER

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